JACC Vol. 27, No. 7
June 1996:1678–87

Intravascular Ultrasound Predictors of Restenosis After Percutaneous Transcatheter Coronary Revascularization

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Objectives. **This study sought to evaluate preintervention and postintervention intravascular ultrasound studies for potential predictors of angiographic restenosis and to use ultrasound predictors of restenosis to enhance our understanding of the pathophysiology of the restenosis disease process.**

Background. **Restenosis remains the major limitation of percutaneous transcatheter coronary revascularization. Although its mechanisms remain incompletely understood, numerous studies have identified some of the clinical, anatomic and procedural risk factors for restenosis. Intravascular ultrasound imaging of target lesions before and after catheter-based treatment consistently demonstrates more target lesion calcium, more extensive reference segment atherosclerosis, smaller final lumen dimensions, significant residual plaque burden and a greater degree of tissue trauma than is evident by angiography.**

Methods. **Intravascular ultrasound studies were performed in 360 nonstented native coronary artery lesions (final diameter stenosis 18 ± 11%) in 351 patients for whom follow-up angiographic data were available 6.4 ± 3.6 months later. Hospital charts were reviewed, and qualitative and quantitative coronary angiographic and intravascular ultrasound analyses were performed by independent core laboratories. Four dependent angiographic end points were tested: restenosis as a binary definition (≥50% diameter stenosis at follow-up) was the primary end point; follow-up diameter stenosis, late lumen loss and follow-up minimal lumen diameter were the secondary end points.**

Results. **Reference vessel size, the preintervention quantitative coronary angiographic assessment of lesion severity and the postintervention intravascular ultrasound cross-sectional measurements predicted the late angiographic results. In particular, the intravascular ultrasound postintervention cross-sectional narrowing (plaque plus media cross-sectional area divided by external elastic membrane cross-sectional area) predicted the primary end point (restenosis) and two of the three secondary end points (follow-up diameter stenosis and late lumen loss) and was therefore the most consistent predictor of restenosis.**

Conclusions. **Intravascular ultrasound variables are more powerful and consistent predictors of angiographic restenosis than currently accepted clinical or angiographic risk factors.**

(J Am Coll Cardiol 1996;27:1678–87)

Restenosis remains the major limitation of percutaneous transcatheter coronary revascularization. Although its mechanisms remain incompletely understood, numerous studies have identified some of the clinical, anatomic and procedural risk factors for restenosis. The clinical variables of diabetes and unstable angina and the angiographic variables of the final minimal lumen diameter or the final diameter stenosis have been the most useful predictors identified to date (1).

Because intravascular ultrasound provides transmural images of coronary arteries in vivo, the normal coronary artery wall, the major components of the atherosclerotic plaque and the serial changes that occur with the atherosclerotic disease process and as a result of transcatheter therapy can be studied in humans in a manner previously not possible (2–6). Previous studies have indicated that intravascular ultrasound imaging of target lesions before and after catheter-based treatment consistently demonstrates more target lesion calcium (7), more extensive reference segment atherosclerosis (8,9), smaller final lumen dimensions (6,10), significant residual plaque burden (11,12) and a greater degree of tissue trauma than is evident by angiography (2).

The purpose of the present study was to evaluate preintervention and postintervention intravascular ultrasound studies for potential predictors of angiographic restenosis and to use ultrasound predictors of restenosis to enhance understanding of the pathophysiology of the restenosis disease process.

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Manuscript received November 1, 1995; revised manuscript received February 5, 1996, accepted February 9, 1996.

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0735-1097/96/$15.00
PII S0735-1097(96)00083-6

Methods

Patients. Between July 1, 1991 and December 30, 1994, intravascular ultrasound studies were performed in 360 nonstented native coronary artery lesions in 351 patients for whom follow-up angiographic data were available 6.4 ± 3.6 months later. Reasons for follow-up angiography included recurrent symptoms (n = 336) or planned follow-up as part of clinical protocols (n = 24, balloon angioplasty arm of the Stent Restenosis Study [STRESS] or the Optimal Atherectomy Restenosis Study [OARS]). Reasons for study exclusion were stent implantation at the lesion site, target lesion calcification extensive enough to preclude accurate cross-sectional vessel quantification or follow-up angiography performed at another institution. The analysis of predictors of angiographic restenosis in these 360 lesions forms the basis of this report.

There were 287 men and 64 women; mean patient age was 60 ± 11 years (range 31 to 85). Target lesion location was left main coronary artery in 16, left anterior descending artery in 169, left circumflex artery in 53 and right coronary artery in 122; 59 (16.3%) of the lesions were ostial in location, and 117 (36.5%) had a history of restenosis. Devices used were balloon angioplasty in 45, directional coronary atherectomy (Devices for Vascular Intervention) in 172, high speed rotational atherectomy (Heart Technology) in 89 and excimer laser angioplasty (Spectranetics/Advanced Interventional Systems) in 54. Adjunctive balloon angioplasty was used in 229 (63.6%), and adjunctive directional coronary atherectomy (after rotational atherectomy or excimer laser angioplasty) in 39 (10.8%).

Clinical and lesion demographics. The hospital charts of all patients were reviewed independently by a registered nurse to obtain clinical demographics and laboratory results. *Angina* was categorized as stable, accelerated, postinfarction or at rest. A *recent myocardial infarction* occurred ≤6 weeks of the study; a *remote myocardial infarction* occurred >6 weeks before the study. In addition, a history of coronary artery bypass surgery (including graft age) and the presence of multivessel coronary artery disease (>50% diameter stenosis in two or more epicardial coronary arteries) were noted.

Risk factors for coronary artery disease that were tabulated included diabetes mellitus (medication dependent, including oral hypoglycemics and insulin), hypertension (medication dependent only), hypercholesterolemia (medication dependent or serum cholesterol ≥240 mg/dl) and smoking (still smoking or having stopped smoking <6 months before the study). Laboratory data recorded included baseline admission hematocrit, platelet count and serum creatinine.

Angiographic analysis. Qualitative and quantitative coronary angiography was performed by an independent core angiographic laboratory with no knowledge of the results of the ultrasound analysis. Standard qualitative angiographic variables were recorded (13). Quantitative coronary angiography was performed using an automated edge detection algorithm (ARTREK, Quantitative Cardiac Systems). Minimal lumen diameter, reference diameter and percent diameter stenosis before and after intervention and on follow-up were measured from multiple projections, and the results from the "worst" view were recorded. *Late lumen loss* was calculated as postintervention minimal lumen diameter minus follow-up minimal lumen diameter. *Target lesion location* was designated as ostial, proximal, mid or distal. *Ostial lesions* were those lesions that began within 3 mm of the major coronary artery ostium. *Lesion length* was measured as the distance (in millimeters) from the proximal shoulder to the distal shoulder of the lesion in the projection that demonstrated the lesion with the least foreshortening. Furthermore, lesions were characterized as *discrete* (<10 mm in length), *tubular* (10 to 20 mm in length) or *diffuse* (>20 mm in length). An *eccentric target lesion* appeared to have three times as much plaque on one side of the lesion as on the other. *Angulation* was present if the centerline through the lumen proximal to the lesion compared to the centerline through the lumen distal to the lesion was >45°. A *tortuous artery* had at least two bends of >60° that had to be traversed to reach the target lesion. An *irregular lesion* had abnormal vessel margins. Specifically, an ulcerated lesion had a small crater or luminal flap, potentially with discrete lumen widening beyond a narrow mouth in the area of stenosis. An *aneurysm* had widening of the lumen beyond the apparent normal contour of the artery. *Calcification* was identified as readily apparent radiopacities within the vascular wall at the site of the stenosis and was classified as *none/mild, moderate* (radiopacities only noted during the cardiac cycle prior to contrast injection) and *severe* (radiopacities noted without cardiac motion before contrast injection). *Flow* was graded according to the Thrombolysis in Myocardial Infarction (TIMI) study criteria. *Postintervention dissections* were identified as breaks in the apparent continuity of the arterial wall.

Initial qualitative and quantitative readings were recorded by a single angiographic technician. Overreading of all cineangiograms was performed at a separate sitting by a single experienced angiographer.

Intravascular ultrasound imaging protocol. Operators were not blinded to the ultrasound images and frequently used the information to make procedural decisions including, but not limited to, device selection. Intravascular ultrasound imaging was performed after administration of 0.2 mg intracoronary nitroglycerin. Before and after the intervention, the ultrasound catheter was advanced ~10 mm beyond the target lesion, and a slow imaging run was performed from beyond the target lesion to the aortoostial junction.

Studies were performed using one of three commercially available systems. The first (CVIS/InterTherapy Inc.) incorporated a single-element 25-MHz transducer and an angled mirror mounted on the tip of a flexible shaft that was rotated at 1,800 rpm within a 3.9F short monorail polyethylene imaging sheath to form planar cross-sectional images in real time; with this system the transducer was withdrawn automatically at 0.5 mm/s to perform the imaging sequence. The second (Hewlett-Packard and Boston Scientific Corporation) incorporated a single-element 30-MHz beveled transducer rotated at 1,800 rpm within a 3.5F short monorail imaging catheter; with this system the catheter was advanced or withdrawn manually

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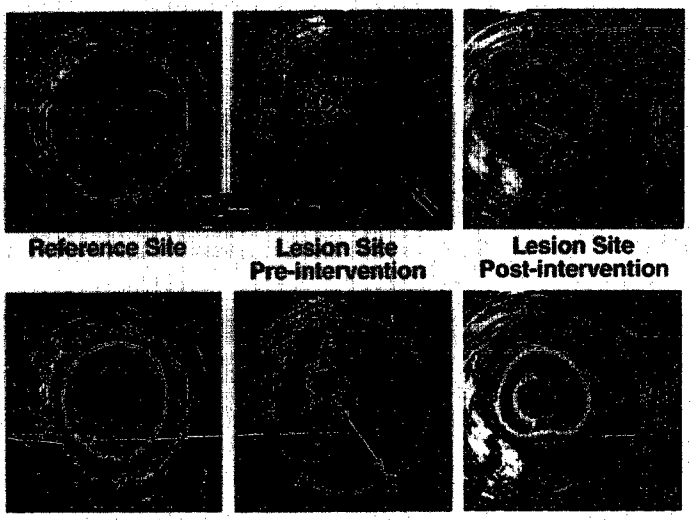

Figure 1. Intravascular ultrasound cross-sectional images accompanied by a duplicate image with an overlay showing the tracing of the lumen (**white line**) and medial-adventitial border (**gray line**). The reference site was the most visually normal cross section within 10 mm proximal to the lesion but distal to any major side branch. In the preintervention images, the catheter (C) was "stuffed" into the lesion; the lesion contained almost exclusively "soft" plaque elements (the plaque elements were less dense than the reference adventitia, shown by the **double white arrows**); and the maximal and minimal plaque thicknesses (**double-headed white arrows and black arrowheads,** respectively) were measured. In the postintervention image, there was a dissection plane (**white arrow**) that extended into the media.

with fluoroscopic guidance to perform the imaging sequence. The third (Cardiovascular Imaging Systems, Inc.) used a single-element beveled transducer mounted on the end of a flexible shaft and rotated at 1,800 rpm within either a 2.9F long monorail/common distal lumen imaging sheath or within a 3.2F short monorail imaging sheath. With this system the transducer was also withdrawn automatically at 0.5 mm/s to perform the imaging sequence. Ultrasound studies were recorded on half-inch high resolution s-VHS tape for off-line analysis.

Patients were studied after giving written, informed consent. Intravascular ultrasound imaging is performed as part of ongoing protocols approved by the Institutional Review Board of the Washington Hospital Center.

Quantitative intravascular ultrasound measurements (Fig. 1). Validation of normal coronary artery anatomy, plaque composition and morphology and measurements of external elastic membrane cross-sectional area, residual lumen cross-sectional area, plaque plus media cross-sectional area and total wall thickness by intravascular ultrasound have been reported previously (14–19). The term external elastic membrane cross-sectional area is short-hand for the area within the border between the hypoechoic media and the echoreflective adventitia, a reproducible measure of total arterial cross-sectional area. Because media thickness cannot be measured accurately, plaque plus media cross-sectional area was used as a measurement of the amount of atherosclerotic plaque (20). Total wall (plaque plus media) thickness was used to calculate the eccentricity index. The cross-sectional narrowing has been alternatively termed the "plaque burden" or the "percent plaque area" by other investigators; it represents the percent of total arterial cross-sectional area occupied by plaque. Significant intravascular ultrasound cross-sectional narrowing (or plaque burden or percent plaque area) can exist in the absence of lumen compromise.

Using computer planimetry, the target lesion was assessed before and after intervention by measuring: 1) lesion site external elastic membrane cross-sectional area (mm^2); 2) lesion site lumen cross-sectional area (mm^2); 3) minimal lumen diameter (mm); 4) plaque plus media cross-sectional area (mm^2) (equals external elastic membrane cross-sectional area minus lumen cross-sectional area); 5) cross-sectional narrowing (%) (equals plaque plus media cross-sectional area times 100 divided by external elastic membrane cross-sectional area); and 6) eccentricity index (equals maximal total wall thickness divided by minimal total wall thickness).

Although acoustic shadowing caused by lesion calcification made identification of the external elastic membrane in some lesions difficult, two types of extrapolation were useful. Briefly, because the cross-sectional geometry of the coronary artery was more or less circular, extrapolation of the circumference of the external elastic membrane was possible provided that each calcific deposit did not shadow more than 60° of the adventitial circumference. Also, real-time axial movement of the transducer just distal and proximal to a calcific deposit (or to find the smallest circumferential arc of calcium within a large calcific deposit) helped unmask and fill in contiguous parts of the adventitia that were otherwise shadowed by that deposit (3,21).

When the atherosclerotic plaque abutted against the catheter, the lumen was assumed to be the size of the imaging catheter; therefore, 0.8 mm^2 was the smallest lumen that could be recorded. An eccentricity index of 1.0 indicated purely concentric target lesion plaque distribution. Preintervention and postintervention intravascular ultrasound studies were compared to calculate acute arterial expansion (increase in

external elastic membrane cross-sectional area) and acute atheroablation (decrease in plaque plus media cross-sectional area) during the procedure.

Target lesion plaque composition was assessed visually (22). The presence of significant amounts of calcium, dense fibrous tissue or soft plaque was tabulated independently for each lesion; for example, a mixed lesion containing both soft and fibrotic plaque elements was tabulated as containing both soft plaque and fibrotic plaque. Calcium produced bright echoes (brighter than the reference adventitia) with acoustic shadowing of deeper arterial structures; its location distribution, and extent were analyzed in detail (7). The location (superficial or deep) of target lesion calcium was defined as *superficial* (calcium at the intimal–lumen interface), *deep* (more than half the distance from the intimal–lumen interface to the external elastic membrane) or *both* (superficial and deep). Calcium was quantified using a protractor centered on the lumen by measuring the 1) total circumferential arc of calcium (in degrees) and 2) superficial arc of calcium (in degrees).

Dense fibrous tissue produced echoes that were as bright as or brighter than the reference adventitia, but without acoustic shadowing. The absence of acoustic shadowing differentiated dense fibrous tissue from calcium.

Soft plaque was less dense than the reference adventitia. Soft plaque is heterogeneous, containing various amounts of loose connective tissue, lipid, intimal hyperplasia or thrombus.

Postintervention dissections were defined as abrupt, focal interruptions in the continuity of the plaque or intima that extends axially, radially or circumferentially, spanning normal tissue planes, particularly if not present on preintervention imaging (2,17,23). Echolucent zones without abrupt breaks in the continuity of the plaque or intima (potentially representing soft plaque elements) were not counted as dissections. Also, echolucent zones at the junction of calcified and noncalcified elements that extended only radially (possibly representing echo dropout) were not counted. The number of distinct dissection planes in each target lesion was counted.

The target lesion lumen was normalized to a proximal reference segment (8). The reference segment was selected as the most normal-looking cross section within 10 mm proximal to the target lesion but distal to a major side branch. In circumstances in which a proximal reference segment could not be identified (e.g., ostial lesion location or diffuse proximal disease extending back to a major side branch), then a distal reference (also within 10 mm of the target lesion, but proximal to a major side branch) was analyzed. Cross-sectional reference site measurements were similar to those made for the target lesion and included the external elastic membrane, lumen and plaque plus media cross-sectional area, cross-sectional narrowing, minimal lumen diameters, eccentricity index and arc of calcium.

Statistics. Statistical analysis was performed using BMDP (24). Continuous data are presented as mean value ± SD, and categoric data are presented as frequencies. Categoric data were compared using chi-square analysis. Continuous variables were compared using the Student *t* test.

Univariate and multivariate logistic regression analysis were used to select the best clinical, angiographic or intravascular ultrasound predictors of angiographic restenosis. Four dependent angiographic variables indicative of restenosis were tested.

The primary end point was the binary angiographic definition of restenosis (defined as a follow-up diameter stenosis ≥50%) (25). Univariate predictors of angiographic restenosis with a p value <0.2 were entered into the multivariate model. A forward elimination and maximum likelihood estimation were used to select the independent predictors of angiographic restenosis. The odds ratios and 95% confidence intervals are presented in the tables for both the univariate predictors and the final multivariate model. An odds ratio >1 means an increased predicted risk for the variable listed; an odds ratio <1 means a decreased risk.

The three secondary angiographic end points were the follow-up diameter stenosis, late lumen loss and the follow-up minimal lumen. Univariate and multivariate linear regression analysis was used to select the best predictors of the follow-up angiographic diameter stenosis and minimal lumen diameter. Univariate predictors of angiographic restenosis with a p value <0.2 were entered into the multivariate model. Forward stepping was used to determine the best predictors of the follow-up angiographic diameter stenosis, late lumen loss and minimal lumen diameter. The correlation coefficient and R value were presented for the final (multivariate) models.

Results

Clinical and historical predictors of restenosis. Clinical demographics in the overall patient cohort were as follows: 30% had diabetes, 47% had hypertension, 65% had hypercholesterolemia, 11% had a history of a recent myocardial infarction, 30% had a history of a remote myocardial infarction, 28% had unstable angina and 26% were smokers. In this patient cohort, patient age, male gender, patient race, hypertension, smoking, diabetes mellitus, unstable angina, multivessel disease, presence of bypass grafts and recent or remote myocardial infarction were not significant univariate predictors of restenosis.

Preprocedural and postprocedural angiographic predictors of restenosis. Lesion demographics in the overall cohort were as follows: 33% were restenotic, 17% were ostial in location, 47% were anterior descending in location, 27% were ≥10 mm in length, 61% were eccentric, 34% were calcified, 19% were irregular, 19% involved branch vessels (were at bifurcation sites), 6% were total occlusions and 11% had TIMI (Thrombolysis In Myocardial Infarction) flow less than grade 3.

Reference vessel size measured 3.10 ± 0.59 mm. Overall, the preintervention minimal lumen diameter measured 0.98 ± 0.52 mm, and the diameter stenosis measured 69 ± 15%. The postintervention minimal lumen diameter increased to 2.62 ± 0.68 mm, and the diameter stenosis decreased to 18 ± 13%. The follow-up interval was 6.4 ± 3.6 (range 1 to 23) months. At follow-up, there was attrition in minimal lumen diameter to

Table 1. Univariate Angiographic Predictors of Restenosis (mean ± SD)

	Total (n = 360)	No Restenosis (n = 157)	Restenosis (n = 203)	OR	95% CI	p Value
Reference site lumen diameter (mm)	3.10 ± 0.59	3.24 ± 0.62	2.98 ± 0.54	0.44	0.30–0.67	< 0.001
Preintervention lesion site						
Lesion length (mm)	8.72 ± 5.38	7.87 ± 4.74	9.39 ± 5.76	1.06	1.01–1.11	< 0.05
Eccentric (%)	60.6	67.6	54.9	0.59	0.37–0.92	< 0.005
MLD (mm)	0.98 ± 0.52	1.12 ± 0.57	0.86 ± 0.45	0.35	0.22–0.56	< 0.001
DS (%)	69 ± 15	65 ± 16	71 ± 14	1.29	1.11–1.50	< 0.001
Postintervention lesion site						
MLD (mm)	2.62 ± 0.68	2.82 ± 0.69	2.46 ± 0.63	0.41	0.30–0.62	< 0.001
DS (%)	18 ± 13	16 ± 13	20 ± 14	1.25	1.05–1.48	< 0.05

CI = confidence interval; DS = diameter stenosis; MLD = minimal lumen diameter; OR = odds ratio.

1.52 ± 0.92 mm, with an associated increase in diameter stenosis to 51 ± 26%; 203 target lesions were classified as restenotic lesions.

Table 1 lists the univariate angiographic predictors of restenosis at the $p < 0.05$ level. Other predictors at the $p < 0.2$ level (and therefore tested in the multivariate model) included 1) the use of rotational atherectomy, 2) lesions >10 mm in length, 3) vessel tortuosity, 4) total occlusion lesions, and 5) preintervention TIMI flow less than grade 3. Left anterior descending or ostial lesion location, target lesion calcification and prior catheter-based intervention were not univariate predictors of restenosis.

Preprocedural and postprocedural ultrasound results and predictors of restenosis. The postintervention improvement in lesion site lumen cross-sectional area (from 1.74 ± 0.92 mm^2 to 6.34 ± 2.52 mm^2, $p < 0.0001$) was caused by a combination of vessel expansion (increase in external elastic membrane cross-sectional area from 19.14 ± 6.47 mm^2 to 20.27 ± 6.59 mm^2, $p < 0.0001$) and tissue ablation (decrease in plaque plus media cross-sectional area from 17.42 ± 6.30 mm^2 to 13.94 ± 5.57 mm^2, $p < 0.0001$). The atherectomy index (contribution of tissue removal to lumen improvement) was 62 ± 52%. The cross-sectional narrowing decreased from 90 ± 5% to 68 ± 11% ($p < 0.0001$). The postintervention intravascular minimal lumen diameter (2.43 ± 0.53 mm) correlated with the postintervention quantitative angiographic minimal lumen diameter ($r = 0.671$, $p < 0.0001$). The postintervention cross-sectional narrowing correlated fairly to poorly with the postintervention angiographic diameter stenosis ($r = 0.381$, $p < 0.0001$).

Table 2 lists the univariate intravascular ultrasound predictors of restenosis at the $p < 0.05$ level. Other predictors at the $p < 0.2$ level (and therefore tested in the multivariate model) included 1) lesion maximal wall (plaque plus media) thickness (2.27 ± 0.56 mm), 2) target lesion calcium (110 ± 107°), and 3) postintervention plaque plus media cross-sectional area. Ultrasound variables that were not predictive at the $p < 0.2$ level included plaque composition (i.e., dominant soft vs. fibrotic vs. calcific plaque), calcium location and arc of superficial calcium, minimal wall thickness, plaque ablation and dissections after intervention.

Table 2. Univariate Intravascular Ultrasound Predictors of Restenosis (mean ± SD)

	Total (n = 260)	No Restenosis (n = 157)	Restenosis (n = 203)	OR	95% CI	p Value
Reference site						
EEM CSA (mm^2)	18.8 ± 7.2	20.1 ± 8.8	17.9 ± 5.5	0.96	0.93–0.99	< 0.05
Lumen CSA (mm^2)	9.5 ± 4.1	10.5 ± 4.8	8.7 ± 3.3	0.89	0.84–0.95	< 0.001
CSN (%)	49 ± 13	47 ± 13	50 ± 12	1.27	1.06–1.51	< 0.01
Preintervention lesion site						
Eccentricity index	3.63 ± 2.62	4.02 ± 2.87	3.43 ± 2.39	0.91	0.82–0.99	< 0.05
Lumen CSA (mm^2)	1.74 ± 0.92	1.91 ± 1.10	1.62 ± 0.74	0.70	0.53–0.92	< 0.05
MLD (mm)	1.38 ± 0.24	1.42 ± 0.28	1.36 ± 0.20	0.35	0.12–0.99	< 0.05
CSN (%)	90 ± 5	89 ± 6	91 ± 5	2.11	127–3.49	< 0.005
Postintervention lesion site						
Lumen CSA (mm^2)	6.34 ± 2.52	7.06 ± 2.66	5.76 ± 2.26	0.81	0.73–0.89	< 0.001
MLD (mm)	2.43 ± 0.53	2.57 ± 0.53	2.32 ± 0.50	0.39	0.25–0.62	< 0.001
CSN (%)	68 ± 11	64 ± 11	71 ± 10	1.80	1.42–2.27	< 0.001
Acute expansion (mm^2)	1.85 ± 1.94	2.23 ± 2.19	1.56 ± 1.68	0.83	0.72–0.96	< 0.05

CSA = cross-sectional area; CSN = cross-sectional narrowing; EEM = external elastic membrane; other abbreviations as in Table 1.

Table 3. Multivariate Predictors of Restenosis, Angiographic Follow-Up Diameter Stenosis, Late Lumen Loss and Angiographic Follow-Up Minimal Lumen Diameter

	Restenosis			F/U DS			Late Lumen Loss			F/U MLD		
	OR	95% CI	p Value	Corr Coeff	R Value	p Value	Corr Coeff	R Value	p Value	Corr Coeff	R Value	p Value
Reference site												
QCA ref diameter (mm)										0.2897	0.5389	< 0.05
IVUS ref lumen CSA	0.89	0.83–0.96	< 0.001							0.0460	0.5829	< 0.01
Preintervention lesion site												
QCA MLD (mm)				−0.1176	0.4145	< 0.001				0.3814	0.5236	< 0.001
QCA DS	1.28	1.07–1.53	< 0.01				0.8371	0.4493	< 0.05			
Postintervention lesion site												
QCA DS							−2.9859	0.3759	< 0.001			
IVUS EEM CSA										−0.0397	0.5635	< 0.001
IVUS lumen CSA										0.1150	0.4526	< 0.001
IVUS CSN	1.67	1.29–2.16	< 0.001	0.7012	0.3455	< 0.001	1.5236	0.4249	< 0.05			

Corr Coeff = correlation coefficient; F/U = follow-up; IVUS = intravascular ultrasound; QCA = quantitative coronary angiography; ref = reference; other abbreviations as in Tables 1 and 2.

Multivariate predictors of angiographic restenosis (Table 3). The quantitative coronary angiographic preintervention assessment of lesion severity (minimal lumen diameter or diameter stenosis) were independent predictors of the follow-up angiographic results.

The postintervention intravascular ultrasound measurements were more powerful predictors of the primary end point (restenosis rate) and secondary end points (follow-up diameter stenosis, late lumen loss and follow-up angiographic minimal lumen diameter) than any of the postintervention quantitative coronary angiographic measurements. In particular, the intravascular ultrasound postintervention cross-sectional narrowing predicted the primary end point (restenosis) and two of the three secondary end points (follow-up diameter stenosis and late lumen loss) and was, therefore, the most consistent predictor of the follow-up angiographic results.

In addition, the quantitative coronary angiographic postintervention diameter stenosis was an independent predictor of late lumen loss. The intravascular ultrasound postintervention lumen cross-sectional area was an independent predictor of the follow-up minimal lumen diameter. Importantly, the intravascular ultrasound postintervention external elastic membrane cross-sectional area was also an independent predictor of the follow-up minimal lumen diameter: the *larger* the external elastic membrane cross-sectional area, the *smaller* was the follow-up minimal lumen diameter.

The mechanism of lumen improvement (acute vessel expansion vs. plaque ablation) was not an important predictor of the late angiographic results.

The reference vessel lumen size (quantitative coronary angiographic reference lumen diameter or intravascular ultrasound reference lumen cross-sectional area), but not the reference vessel external elastic membrane cross-sectional area or the reference segment plaque burden (cross-sectional narrowing), was also an important predictor of the follow-up angiographic results.

Discussion

Retrospective analyses of clinical and angiographic studies in the past decade have identified several risk factors for restenosis after coronary angioplasty. These can be classified into 1) patient-related factors, such as gender, history of restenosis, diabetes, hyperlipidemia, hypertension, unstable angina, vasospastic angina, end-stage renal disease and continued smoking (26–33); 2) procedure-related factors, such as balloon/artery ratio, presence of significant residual translesion gradient, small residual lumen, significant residual stenosis and extent of dissection (26,27,34–36); and 3) lesion-related factors, such as pretreatment vessel size, severity of pretreatment stenosis, calcification, eccentricity, saphenous vein graft lesion location, ostial or proximal lesion location, left anterior descending lesion location, chronic total occlusions and long lesion length (25–28,34,37–42). In the current study, the univariate angiographic risk factors for restenosis were similar to those found in previously published findings. In addition, the current study identified the univariate intravascular ultrasound predictors of angiographic restenosis.

In the multivariate analysis, four dependent angiographic end points were used: restenosis as a binary definition (≥50% diameter stenosis at follow-up) was the primary end point; the follow-up diameter stenosis, late lumen loss and the follow-up minimal lumen diameter were the secondary end points. In these multivariate analyses (that also tested the previous independent clinical, procedural and lesion-based angiographic variables), the intravascular ultrasound measurements were the most powerful predictors of subsequent angiographic restenosis.

Angiographic results. Reference vessel size measured 3.10 ± 0.59 mm. In this study cohort, the angiographic reference vessel size was a predictor of the follow-up minimal lumen diameter but not of restenosis, late lumen loss or the follow-up angiographic diameter stenosis. There are several

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possible explanations for the failure of angiographic reference vessel size to predict restenosis in this analysis: 1) Angiography was not the only measure of the reference lumen size; the intravascular ultrasound reference lumen cross-sectional area, which was also tested in the analyses, predicted both restenosis and the follow-up minimal lumen diameter. 2) The angiographic reference lumen diameter reflects both vessel size and overall extent of disease; it increases in proportion to increasing vessel size and decreases in proportion to the extent of atherosclerosis. 3) Intravascular ultrasound directly measures both vessel size (reference segment and target lesion external elastic membrane cross-sectional area) and extent of atherosclerosis (reference segment disease and target lesion cross-sectional narrowing).

The final (postprocedural) angiographic diameter stenosis measured 18 ± 13%. The predictive value of the angiographic results may have been blunted by the overall quality of the angiographic results. However, it is known that angiography may underestimate the severity of the residual postprocedural lumen compromise (6,10). This is substantiated by the only fair correlation between intravascular ultrasound and quantitative angiographic measurement of minimal lumen diameter found in this study. Irregular lumen shapes and postintervention dissection planes (which are readily incorporated into the angiographic lumenogram but are easily excluded from the intravascular ultrasound cross-sectional measurements) are frequent confounders in coronary angiography.

Although the postprocedural intravascular ultrasound assessment may be useful in determining the cause of a suboptimal angiographic result, this study shows that it may be even more useful in patients with a good angiographic result. Despite a final angiographic diameter stenosis of 18 ± 15%, the intravascular ultrasound cross-sectional narrowing measured 68 ± 11% and was the most important predictor of restenosis.

Intravascular ultrasound results. Univariate intravascular ultrasound predictors of restenosis included 1) reference vessel size [total arterial (external elastic membrane) and lumen cross-sectional area] and cross-sectional narrowing; 2) target lesion plaque distribution (eccentricity index); 3) target lesion preintervention and postintervention lumen cross-sectional area and minimal lumen diameter and cross-sectional narrowing; and 4) the magnitude of acute expansion during the interventional procedure. Plaque composition, absolute plaque mass (plaque plus media cross-sectional area) preintervention or postintervention or at the reference site and tissue disruption or plaque ablation during the interventional procedures were not predictors of restenosis. Both plaque ablation (by decreasing plaque plus media cross-sectional area) and vessel expansion (by increasing external elastic membrane cross-sectional area) will decrease the residual cross-sectional narrowing.

In the various multivariate models, the only intravascular ultrasound predictors of late angiographic results were 1) the reference vessel size (reference lumen cross-sectional area); 2) the lesion site postintervention external elastic membrane and lumen cross-sectional areas; and, most important, 3) the lesion site postintervention cross-sectional narrowing. The preintervention intravascular ultrasound quantitative assessment was less important than the preintervention quantitative angiographic assessment of lesion severity and lumen dimensions, presumably because intravascular ultrasound cannot measure lumen dimensions smaller than the imaging catheter; therefore, the power of the preintervention intravascular ultrasound assessment is lost in more severe stenoses. The reference segment plaque burden (cross-sectional narrowing) appears to be less important than the postintervention lesion site plaque burden (cross-sectional narrowing), indicating that what happens at the lesion site dominates the follow-up period after intervention, at least within the restenosis time frame (8). This is in contradistinction to the findings of other investigators (43).

Importance of intravascular ultrasound cross-sectional narrowing. Our intravascular ultrasound findings suggest that the residual cross-sectional narrowing (the percent of total arterial cross-sectional area occupied by atherosclerotic plaque at the conclusion of the procedure) may be a more powerful predictor of restenosis than standard clinical or angiographic variables. This is a measurement that is unique to intravascular ultrasound and has no angiographic equivalent. There are three potential explanations for the importance of the intravascular ultrasound cross-sectional narrowing.

1. As indicated previously, previous studies have shown that important angiographic predictors of restenosis are vessel size and the postprocedural minimal lumen diameter and diameter stenosis. The intravascular ultrasound postintervention cross-sectional narrowing includes a measure of both the vessel size (external elastic membrane cross-sectional area) and final lumen dimensions (lumen cross-sectional area): external elastic membrane cross-sectional area minus lumen cross-sectional area divided by external elastic membrane cross-sectional area.

2. Recent studies from our laboratory have shown that the direction and magnitude of arterial remodeling (a change in total arterial or external elastic membrane cross-sectional area) are the major determinants of late responses to transcatheter therapy, including restenosis (44). The impact of arterial remodeling on lumen dimensions may be related to the severity of the underlying lesion; and mathematically, it can be shown that the impact of a change in arterial cross-sectional area is magnified by the residual cross-sectional narrowing. For example, in normal arteries, a 50% decrease in arterial (external elastic membrane) cross-sectional area would be necessary to produce a 50% decrease in lumen cross-sectional area. Conversely, in arteries with a significant residual cross-sectional narrowing, even a small decrease in arterial (external elastic membrane) cross-sectional area would have a profound impact on lumen cross-sectional area. For example, if, as in the current study, the postintervention cross-sectional narrowing averaged 68%, a 45% to 60% late lumen loss would require only a 15% to 20% decrease in arterial (external elastic membrane) cross-sectional area (45). This is shown schematically in Figure 2. The interrelation between the final cross-

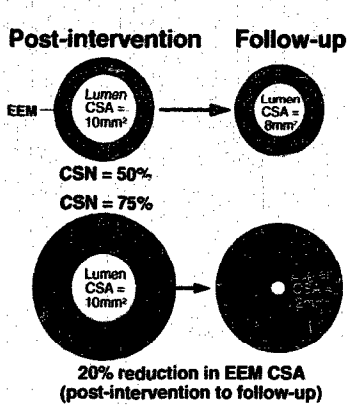

Figure 2. Interaction of the residual cross-sectional narrowing (CSN) and arterial remodeling on restenosis is shown by comparing two theoretic lesions, both with the same residual lumen cross-sectional area (CSA) of 10 mm^2. **Upper lesion,** The postintervention cross-sectional narrowing was 50% (i.e., the postintervention external elastic membrane [EEM] cross-sectional area would have measured 20 mm^2). Assuming a 20% reduction in external elastic membrane cross-sectional area from postintervention to follow-up, the follow-up lumen cross-sectional area would have decreased from 10 to 8 mm^2. **Lower lesion,** The postintervention cross-sectional narrowing was 75% (the postintervention external elastic membrane cross-sectional area would have measured 40 mm^2). Again, assuming the same 20% reduction in external elastic membrane cross-sectional area from postintervention to follow-up, the follow-up lumen cross-sectional area would have decreased from 10 to 2 mm^2. This explains the importance of the residual cross-sectional narrowing (and the size of the external elastic membrane for any given residual lumen cross-sectional area) as a predictor of restenosis.

sectional narrowing and the long-term results is further substantiated by the finding that the final external elastic membrane cross-sectional area is an independent predictor of the follow-up angiographic minimal lumen diameter: the larger the final external elastic membrane cross-sectional area, the smaller the follow-up angiographic minimal lumen diameter. Thus, these findings validate the importance of arterial remodeling as a mechanism of restenosis.

3. Restenosis may be related to extent of disease. Extensive disease may impact on reference lumen measurements once the ability of the artery to remodel is outstripped; this is represented by the measurement of reference segment cross-sectional narrowing. Similarly, the extent of disease is reflected not only by the reference segment cross-sectional narrowing but also by the target lesion cross-sectional narrowing before and after intervention. Previously, we have shown that the reference segment cross-sectional narrowing and the lesion site cross-sectional narrowing may be interrelated (8).

Clinical and procedural implications: caveats. The ability to identify intravascular ultrasound predictors of restenosis does not necessarily mean that an interventional strategy based on modifying these parameters will reduce restenosis. An overly aggressive interventional strategy designed to maximize the lumen area and minimize the residual cross-sectional narrowing may cause undue vessel trauma. Rather than reducing restenosis, this could lead to an increase in short- and long-term procedural complications. For example, one single-center experience has showed that an aggressive multidevice interventional approach designed to reduce the residual cross-sectional narrowing actually increased restenosis (Tobis JM, unpublished observations). Conversely, the Optimal Atherectomy Restenosis Study (OARS) involved an ultrasound-guided directional coronary atherectomy strategy to maximize lumen dimensions and minimize residual cross-sectional narrowing. The final results of the OARS study (which contained angiographic and intravascular ultrasound as well as clinical end points) are pending; however, the preliminary restenosis rate is less than 30% (46).

Study limitations. Although this study represents a consecutive series of patients studied preintervention and postintervention in whom follow-up angiography was available, it is a study of patients presenting for follow-up largely because of symptomatic recurrence. Thus, because of the nature of the "clinical" follow-up, it may represent a skewed population of patients with good angiographic results and an increased rate of restenosis, and no conclusion about the absolute restenosis rate (which was 56%) should be inferred from this data.

The present study is largely a study of lesions treated with new angioplasty devices with the exception of stents. These findings may or may not be applicable to lesions treated only with balloon angioplasty. Nevertheless, even in the subpopulation of lesions in this study treated with balloon angioplasty, nonrestenotic lesions had a lower cross-sectional narrowing (73 ± 7) than restenotic lesions (77 ± 7, $p < 0.0001$). Furthermore, the angiographic results in this group were excellent (final diameter stenosis of $18 \pm 13\%$). Thus, some patients with less optimal angiographic results went on to be treated with stent implantation and, therefore, were excluded from this study.

The present study was not able to identify device-related differences in restenosis mechanisms. Multiple devices were used, and devices were usually followed by adjunct percutaneous transluminal coronary angioplasty or were used in various combinations depending on lesion morphology. Furthermore, all devices work by a combination of mechanisms, including acute vessel expansion, plaque ablation or redistribution and dissection (even though the relative contributions of each effect may differ among devices) (2–6,47).

The operators were not blinded to the results of the preintervention or postintervention ultrasound studies. Thus, the interventional strategy elected was often determined by plaque composition and distribution as well as by vessel size; and in some procedures attempts were made to optimize the final results according to the ultrasound findings, including maximizing the lumen dimensions, minimizing the residual cross-sectional narrowing and treating intravascular ultrasound-detected dissections. Results in patients treated with angiographic guidance alone might be different. However, the preliminary results of phase II of the Guidance by Ultrasound Imaging for Decision Endpoints (GUIDE) Trial (a multicenter study, with blinded postinterven-

tion imaging in which only angiographic guidance was used) has come to virtually the same conclusion. In phase II of the GUIDE Trial, the ultrasound findings, particularly the residual cross-sectional narrowing, were the most powerful predictors of restenosis (48).

Last, both stented lesions and some heavily calcified lesions were excluded. Stents were excluded from this analysis for two reasons. Measurement of external elastic membrane cross-sectional area and, therefore, cross-sectional narrowing is difficult in stented lesions because the stent often shadows the deeper adventitial structures. Also, and probably more important, stents reduce restenosis by eliminating arterial remodeling (49–51). Thus, the results and implications in stented versus nonstented lesions are likely to be different. Similarly, measurement of the external elastic membrane cross-sectional area is difficult in some (but not all) heavily calcified lesions (3,4,47).

Conclusions. In a multivariable clinical, angiographic and intravascular ultrasound model of 360 native vessel target lesions in 351 patients, the intravascular ultrasound variables analyzed were more powerful predictors of subsequent angiographic restenosis than currently accepted clinical or angiographic risk factors. The only consistent independent predictor of the follow-up angiogram was the intravascular ultrasound postprocedural cross-sectional narrowing. The mechanism by which a low postprocedural cross-sectional narrowing was achieved (either plaque removal or vessel expansion) did not seem to be important. Mathematically, the importance of the postintervention lesion site cross-sectional narrowing may be its relation to remodeling (change in arterial cross-sectional area) as a mechanism of restenosis. However, the clinical utility of these findings will depend on future studies designed to test the hypotheses that 1) maximizing ultrasound end points (i.e., minimizing the final cross-sectional narrowing) will lead to a reduction in the frequency of restenosis, or 2) that lesions with good angiographic results but a large residual ultrasound cross-sectional narrowing require additional intervention (e.g., stent implantation).

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